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a3 16. (**New**) The method of claim 15, wherein the fibrin monomer composition comprises acid-solubilized fibrin, and the polymerizing agent comprises an amount of base effective to sufficiently neutralize the mixture to allow the fibrin to polymerize. --

REMARKS

Reconsideration of the rejections is respectfully requested. By the present amendment, claims 1-3 are amended, claims 5-12 are cancelled, and new claims13-16 are presented. Thus, claims 1-4 and 13-16 are under examination.

The claims have been amended to more clearly define the invention. Support for the amendments is either apparent, or is as described in the text below. Support for "pliable" is found, for example, at Specification 17: 13-16. Support for adherence is found, for example, at Specification 2: 9-11, 6: 15-16 and 19:16-19.

Asserted Double Patenting

The Office Action asserts that claims 1 and 2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting. No claims have issued in the cited copending application, and Applicant respectfully submits that no claims of sufficient overlap shall issue in the cited copending application.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 1 and 2, as well as 3 and 4, stood rejected under 35 U.S.C. §112, first paragraph, based on an assertion of lack of enablement. This rejection is respectfully traversed.

As to claims 1 and 2, in one aspect the rejection asserts that the specification "fails to provide sufficient guidance or demonstrate any data for the genetic transformation of any nucleic acid, DNA or RNA in any type of cell or subject *in vitro* or *in vivo* via fibrin gel." The specification describes in detail an exemplary fibrin gel, and methods of incorporating the transforming composition into a fibrin gel adhered to cells. Given this, it appears that the Office's assertion is that the invention does not work. In other words, the rejection is for lack of

utility, framed under 35 U.S.C. §112. Given a rejection for lack of utility, Applicant notes that the Office's internal rules require:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the prima facie showing of no specific and substantial credible utility. *If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.*

Revised Utility Examination Guidelines, Federal Register, Volume 64, Number 244, December 21, 1999 (emphasis added). Applicant respectfully submits that the rejection does not specifically explain a scientific basis to doubt the Applicant's utility.

Instead, the Office Action turns the burden, which the Office's rules specifically places on itself, onto the Applicant, requiring proofs that are not part of the patent law. For instance, Office asks the Applicant to explain "how the nucleic acid entrapped in fibrin gel can be taken up by cells." Applicant respectfully notes that even the most skilled in the art can offer no more than informed speculation on the mechanism of transformation. It is not a requirement of the patent law that the applicant understand the theory of operation for his or her invention.

Implicit in the Office's assertion is a belief that the nature of a fibrin gel would somehow disable transformation. That *belief* is not shared by the Applicant. Moreover, the Office's guidelines require that the Office explain any reasoning behind this belief, so that Applicant has a real opportunity to respond.

The Office further asserts that the specification is defective for not teaching how to determine the fact of transformation. Applicant respectfully reminds the Office that it is not the role of the specification to teach what is well known in the art. The methods in question have been known since the early dawn of molecular biology, when bacteriophages were used to identify nucleic acid as the genetic material, and became facile with tools developed at least two decades ago. Numerous catalogs of molecular biology tools provide nucleic acids with marker genes that provide, for example, the phenotype of surviving in a given hostile environment, assayable enzymes, or fluorescent products. An applicant for a bicycle would not have to

describe how to ride that vehicle; and similarly, the present Applicant need not provide the well-known assay protocols available from suppliers such as Promega or Invitrogen, or from standard texts such as are available from Cold Spring Harbor Press.

The Office additionally asserts that no "description of any vector suitable with fibrin as claimed is present in the as filed specification." Again, the burden has been shifted. Nothing in the Office Action supports the implied assertion that the effectiveness of a given vector would be compromised if delivered according to the invention. Applicant respectfully submits that any number of the vectors described in the many gene therapy articles cited in the specification (and incorporated by reference), or commercially available from numerous vendors will be effective in an appropriate context (e.g., in cells where the promoters utilized by the vector can be expected to operate). The Office is reminded that its burden is to provide scientific evidence and reasoning that is "more likely than not a person skilled in the art would not consider credible" Applicant's assertion.

Accordingly, in light of the above discussion, Applicant respectfully submits that the rejection of claims 1 and 2 is in error, and should be withdrawn.

As to claims 3 and 4, the Office Action asserts, among other things:

> The specification fails to provide an enabling disclosure for gene therapy using any nucleic acid in any vector under the control of any promoter for the treatment of any disease or disorder in any subject including human beings, mammals, fish, bird, insect, fungus, plant. The specification fails to provide guidance or demonstrate any data of any therapeutic effect of any gene therapy using any recombinant cells, such as recombinant stem cells, which are transformed by nucleic acid in any vector under the control of any promoter for the treatment of any disease or disorder in any subject.

Again, this appears to be in effect an assertion of lack of utility, with the burden to make the case for utility improperly placed on the Applicant.

The first thing that should be borne in mind is that Applicant is not claiming gene therapy *per se,* but instead a tool for use in gene therapy. The issue is how well the tool is enabled. Gene therapy, for all the complex issues that may arise in the design of gene therapy, has been therapeutically effective. Numerous tools to further address the complex issues of gene therapy

had been constructed by the time Applicant made the presently claimed invention, further rendering these issues addressable without undue experimentation. Nonetheless, no matter how hard gene therapy may be, the literature shows that it is doable.[2] Applicant claims a physical procedure to add to a gene therapy procedure, and has described all that is needed to effect this physical procedure. It is not the law, for example, that the innovator of an improved polymer curing process must anticipate all the polymer contexts in which the process may be used; it is enough that contexts for use are known.

Controlling legal authority on pharmaceutical utility states:

> In the pharmaceutical arts, our court has long held that practical utility may be shown by adequate evidence of any pharmacological activity. * * * Such activity constitutes a practical utility because "[i]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."

Fujikawa v. Wattanasin, 93 F.3d 1559, 1564, 39 USPQ2d 1895, 1899 (Fed. Cir. 1996) (citing *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980); *In re Krimmel*, 292 F.2d 948, 952-53, 130 USPQ 215, 219 (CCPA 1961)). The issues surrounding gene therapy have been in relation to how to make the delivery of the therapeutic gene with sufficient

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[2] See, for example:
as to treating immunodeficiency adenine deaminase deficiency:
Morgan et al., *BMJ* 1999 Nov 13: 319(7220)1310;
Onodera et al., *Acta Haematol.* 101(2): 89-96, 1999;
as to treating cancer in an animal model:
Costantini et al., *Gene therapy* 7(2): 93, 2000;
as to treating brain disorders in animal models:
Wildner et al., *Gene Therapy* 6(1): 57-62, 1999 (Jan);
as to treating Severe Combined Immunodeficiency (SCID)-Xa Disease:
Cavazzana-Calvo et al., *Science* 288: 669-672, 2000;
Kolata, *New York Times* 2000 April 28 (discussing Cavazzana-Calvo et al.);
as to treating hemophilia B:
Wade, *New York Times* 2000 April 28.
Copies of these documents are enclosed as Exhibits A-G, respectively.

specificity, while avoiding adverse problems due to the delivery method. The issues typically have not dealt with whether an appropriate pharmaceutical activity has been targetted; this is typically a given, or at least a safe inference from strong evidence. Thus, in the many contexts where at least exploratory gene therapy protocols have been, and will continue to be, approved by appropriate regulatory authorities, the Federal Circuit's requirement for utility has and will be met. Thus, even assuming arguendo that Applicant had to show broader end use utility, such utility exists: Applicants can deliver a pharmacological activity that provides a practical utility.

As the Office should be well aware, recombinant manipulations using human, mammalian, avian, arthropod, fungal and plant cells are all well known. Thus, there can be no reasonable assertion that the invention cannot be practiced in these and other genera without undue experimentation.

As to the assertion that more guidance is needed to identify vectors and promotors, Applicant again submits that any number of the vectors and promoters described in the many gene therapy articles cited in the specification, or commercially available from numerous vendors, will be effective in an appropriate context.

The Office's assertions as to the unpredictability of gene therapy again miss the mark, given what the Applicant claims. Applicant claims a tool for use in gene therapy, with ample explanation of how to make and use the tool. The tool can be used in the methods of fully successful gene therapies, and in gene therapies that provide appropriate pharmacological activity, even if a clinical trial has not yet shown clear end-point efficacy in humans.

The Office Action cites a.1992 article on the limited availability of embrionic stem cells at that time. However, stem cells are, and Applicant respectfully submits have been, available in amounts allowing the treatments recited in the claims. In the Cavazzana-Calvo et al. article (Exhibit E), the results indicated transformation of stem cells. As indicated in the remarks of the corresponding author and Dr. Stuart Orkin in the *New York Times* article of Exhibit F, the advance that allowed for this predated the results reported by Cavazzana-Calvo et al. Stem cell transformation required, as the successful avenue employed by Cavazzana-Calvo et al., the use of a Moloney viral vector. Vectors of this type are described in the present application. The Office should note further that the pharmacological soundness, and hence utility, of stem cell

gene therapy had been sufficient to justify regulatory approval of the Cavazzana-Calvo et al. clinical trial.

Accordingly, in light of the above discussion, Applicant respectfully submits that the rejection of claims 3 and 4 is in error, and should be withdrawn.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 1 and 2, as well as 3 and 4, stood rejected under 35 U.S.C. §112, second paragraph, based on an assertion that the claims were incomplete for allegedly omitting essential steps, with the alleged omission amounting to a gap between the steps. The Office cites MPEP §2172.01. This rejection is respectfully traversed.

MPEP §2172.01 points out that the issue is whether a claim points out and distinctly claims its subject matter. This is the basic statutory basis for a rejection under 35 U.S.C. §112, second paragraph. The asserted rejection cannot countervail the basic patent law concept that it is not necessary that a claim recite each and every element needed for the practical realization of the claimed subject matter. *Carl Zeiss Stiftung v. Renishaw plc*, 945 F.3d 1173, 20 USPQ 1094 (Fed. Cir. 1991). With these rules in mind, Applicant respectfully submits that one of ordinary skill would recognize what is being claimed in the claims at issue, and hence the claims satisfy 35 U.S.C. §112, second paragraph.

As to claims 1 and 2, the Office asserts that the omitted steps "are: for example, how to determine [that] the cells are transformed with nucleic acid." Applicant respectfully notes there are numerous ways make this determination, and all fall within the scope of the claim. There is no ambiguity.

As to claims 3 and 4, the Office asserts that the omitted steps "are: for example, what type of transformed cells containing which recombinant nucleic acid are used, what kind of diseases or disorders are intended, and whether the implanted transformed cells are present long enough to [secrete] therapeutic effective amount of therapeutic product into the implanted site to exhibit therapeutic effect on the subject. Nothing listed by the Office manifests an ambiguity in claim scope. Applicant claims a very specific tool for gene therapy, applicable in all the contexts noted by the Office. Again, there is no ambiguity.

Accordingly, Applicant respectfully submits that the rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §103(a)

Claim 2 stood rejected under 35 U.S.C. §102(e), based on an assertion of anticipation by the disclosure of Donovan, US Patent 5,833,651. Applicant respectfully traverses.

Donovan discloses a intraluminal stent that is seated in a blood vessel by balloon angioplasty, where the stent is coated with a fibrin composition containing a virus for gene therapy. A careful review of Donovan will show that the fibrin is provided on the stent as a mature clot that allows for "sustainable delivery of virus to cells accessible to a body lumen" (4: 51-52). The teachings even go so far a to recommend contacting the fibrin with heparin (8:66-9:28), an inhibitor of the type of fibrin polymerization taught by Applicant, thereby further confirming that Donovan is about viruses in mature, nonadhesive, nonpliable fibrin polymer. Reference to the Examples of Donovan further confirms this understanding. Applicant respectfully submits that nothing in Donovan discloses adhering a nucleic acid-containing composition to a target cell with fibrin. Donovan is only about an open mesh, biocompatable, holding material for sustained release.

Accordingly, Applicant respectfully submits that the rejection is in error and should be withdrawn.

Conclusion

In light of the above discussion and amendments, it is respectfully submitted that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[3]

Respectfully submitted,

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